Dynamic covalent templated-synthesis of [c2]daisy chains

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SUPPORTING INFORMATION

Revised Version

Table of Contents

1. General Methods.................................................................S2
2. Synthesis.........................................................................S2
3. Molecular Modeling..............................................................S9
4. References..........................................................................S10
5. 1H and 13C NMR Spectra..........................................................S11
6. Analytical High Performance Liquid Chromatography.................S19
1. General Methods

Compounds $1^{S1}$, $2^{S1}$, and $M^{S2}$ were synthesized following the procedures reported in the literature. Anhydrous CH$_2$Cl$_2$ was obtained from a SC Water USA Glass Contous Seca Solvent System. Anhydrous EtOH and anhydrous Et$_3$N were purchased from Aldrich and handled under an atmosphere of dry nitrogen. CDCl$_3$ and CD$_3$CN were obtained from Aldrich and used without further purification. All other reagents were purchased from commercial sources and used without further purification. All reactions were carried out under an atmosphere of dry nitrogen and anhydrous solvents were used, unless otherwise stated. Reactions were monitored by thin layer chromatography using Merck TLC Silica gel 60 F$_{254}$ and the plates were inspected by 254 nm UV light and/or 2,4-DNP, iodine, and KMNO$_4$ stains. Flash column chromatography was performed over Merck Silica gel 60F (230-400 mesh ASTM). Analytical high performance liquid chromatography (HPLC) were performed on reversed phase HPLC (RP-HPLC) instruments, using C$_{18}$ columns and a binary solvent system, i.e., MeCN and H$_2$O with 0.1% (v / v) trifluoroacetic acid. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker ARX-500 (operating at 500 MHz for $^1$H NMR and 125 MHz for $^{13}$C NMR) spectrometer in CDCl$_3$ and CD$_3$CN. All spectra were recorded at 25°C and coupling constants ($J$ values) are given in Hz. Chemical shifts are given in parts per million (ppm). Abbreviations used to define multiplicities are as follows: s = singlet; d = doublet; t = triplet; q = quarter; m = multiplet; br = broad. ESI-Mass spectra were recorded on a Thermo Finnigan LCQ Advantage mass spectrometer. High-resolution mass spectra were measured on an Agilent (Wilmington, DE) 6210 TOF-LC/MS mass spectrometer.

2. Synthesis

![Scheme S1. Synthesis of compound 3](image)

Scheme S1. Synthesis of compound 3
3: Compound 2 (8.96 mmol, 2 g) and 3,5-dimethoxybenzyl amine (8.96 mmol, 1.50 g) were added to a 250 mL round-bottomed flask containing EtOH (100 mL) and the resulting solution was stirred for 24 h at room temperature. NaBH₄ (18 mmol, 0.67 g) was added and the reaction mixture was stirred for additional 24 h before H₂O (1 mL) and K₂CO₃ (1 g) were added to quench reduction. Solvent was removed in vacuo and the residue was taken up in H₂O (100 mL), extracted with EtOAc (3 x 100 mL), and the combined extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, CH₂Cl₂/MeOH, 95:5) to afford 3 as a colorless viscous oil (2.28 g, 80%). ¹H NMR (500 MHz, CDCl₃, 298 K): δ 7.20 (s, 2H), 6.50 (d, J = 2.1 Hz, 2H), 6.37 (t, J = 2.2 Hz, 1H), 4.75 (s, 4H), 3.85 (s, 2H), 3.80 (s, 6H), 3.76 (s, 2H). ¹³C NMR (125 MHz, CDCl₃, 298 K): δ 160.9, 158.5, 151.2, 142.1, 118.5, 106.0, 98.9, 64.4, 55.4, 53.4, 51.8. MS (ESI): m/z Calcd for [M + H]⁺: 319.17; found: 319.50.

4: A solution of 9-fluorenylmethyl chloroformate (Fmoc-Cl) (7.54 mmol, 1.95 g) in 1,4-dioxane (20 mL) was added to a solution of 3 (6.28 mmol, 2 g) in 1,4-dioxane (10 mL) and 10% Na₂CO₃(aq) (20 mL). The mixture was stirred at room temperature for 16 h, poured into H₂O (250 mL) and extract...
mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, CH₂Cl₂/MeOH, 98:2) to afford 4 as a slightly yellow oil (3.05 g, 90%). Because of the restricted rotation about amide bond in the structure, all protons and carbons exhibit two different signals. ¹H NMR (500 MHz, CDCl₃, 298 K): δ 7.75 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.32–7.42 (m, 6H), 7.19–7.27 (m, 4H), 7.00 (s, 2H), 6.75 (s, 2H), 6.39 (s, 1H), 6.37 (s, 1H), 6.33 (s, 2H), 6.25 (s, 2H), 4.74 (s, 4H), 4.69 (s, 4H), 4.61 (d, J = 5.3 Hz, 2H), 4.55 (d, J = 6.5 Hz, 2H), 4.47 (s, 2H), 4.40 (s, 2H), 4.36 (s, 2H), 4.26 (t, J = 6.5 Hz, 1H), 4.19 (br, s, 3H), 3.75 (br, s, 12H). ¹³C NMR (125 MHz, CDCl₃, 298 K): δ 161.2, 161.0, 159.0, 158.9, 156.4, 148.6, 148.4, 143.7, 141.3, 139.0, 127.8, 127.7, 127.1, 125.0, 124.5, 124.0, 118.0, 117.0, 106.2, 105.3, 99.3, 99.2, 68.1, 67.4, 64.4, 64.3, 60.5, 55.4, 50.8, 50.2, 49.3, 48.5, 47.2, MS (ESI): m/z Calcd for [M + H]⁺: 541.23; found: 541.52.

Scheme S3. Synthesis of compound 5

5: Compound 4 (5.54 mmol, 3 g) and IBX (22.16 mmol, 6.20 g) were added to a 250 mL round-bottomed flask containing CH₂Cl₂ (150 mL) and the resulting suspension was heated under reflux until TLC analysis indicated that 4 had been consumed. The reaction mixture was cooled
to room temperature and filtered through celite. H₂O (250 mL) was added to the filtrate and extracted with CH₂Cl₂ (3 x 100 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, CH₂Cl₂) to afford 5 as a slightly yellow solid (2.68 g, 90%). Because of the restricted rotation about amide bond in the structure, all protons and carbons exhibit two different signals.¹H NMR (500 MHz, CDCl₃, 298 K): δ 10.2 (s, 2H), 10.1 (s, 2H), 7.95 (s, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.45–7.55 (m, 6H), 7.40 (m, 4H), 7.15–7.3 (m, 6H), 6.40 (s, 1H), 6.32 (s, 1H), 6.25 (s, 2H), 6.22 (s, 2H), 4.72 (d, J = 4.4 Hz, 2H), 4.62 (s, 2H), 4.56 (d, J = 6.6 Hz, 2H), 4.42 (s, 4H), 4.28 (t, J = 6.4 Hz, 1H), 4.10 (m, 1H), 4.07 (s, 2H), 3.72 (br, s, 12H). ¹³C NMR (125 MHz, CDCl₃, 298 K): δ 191.2, 161.3, 161.1, 156.1, 153.2, 152.9, 150.5, 143.6, 143.5, 141.3, 141.1, 138.5, 127.8, 127.6, 127.2, 127.1, 124.9, 124.1, 123.9, 122.5, 120.1, 119.8, 106.2, 105.4, 99.5, 99.4, 68.4, 66.9, 55.3, 51.6, 50.9, 49.4, 48.6, 47.2, 47.1. MS (ESI): m/z Calcd for [M + H]⁺: 537.20; found: 537.52.

![Scheme S4. Synthesis of P1](image)
**P1**: Morpholine (10 mL) was added to a solution of 5 (3.73 mmol, 2 g) in CH₂Cl₂ (20 mL) and the resulting reaction mixture was stirred at room temperature for 1 h, poured into H₂O (100 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO₂, CH₂Cl₂/MeOH, 95:5) to afford P1 as a colorless oil (0.35 g, 30%). ¹H NMR (500 MHz, CDCl₃, 298 K): δ 10.1 (s, 2H), 8.15 (s, 2H), 6.45 (d, J = 2.1 Hz, 2H), 6.30 (t, J = 2.2 Hz, 1H), 3.90 (s, 2H), 3.79 (s, 2H), 3.72 (s, 6H). ¹³C NMR (125 MHz, CDCl₃, 298 K): δ 192.5, 161.0, 153.1, 152.9, 124.6, 106.0, 99.3, 66.4, 55.4, 53.3, 51.1. MS (ESI): m/z Calcd for [M + H]+: 315.13; found: 315.45.

**Scheme S5. Synthesis of DC1·2CF₃CO₂**

**DC1·2CF₃CO₂**: P1 (0.016 mmol, 5 mg) and M (0.016 mmol, 6 mg) were dissolved in CD₃CN (1 mL) containing an equimolar amount of TFA. The resulting slightly yellow solution was used for characterization. ¹H NMR (500 MHz, CD₃CN, 298 K): δ 10.05 (br, s, 4H), 8.4 (s, 4H), 7.95 (s, 4H), 7.35 (t, J = 7.5 Hz, 4H), 7.20 (d, J = 7.5 Hz, 4H), 6.98 (d, J = 7.5 Hz, 4H), 6.80 (d, J = 7.5 Hz, 4H), 6.17 (d, J = 7.5 Hz, 2H), 6.15 (d, J = 7.5 Hz, 4H), 5.00 (m, 4H), 4.65 (m, 4H), 4.35–4.45 (m, 8H), 3.95–4.20 (m, 8H), 3.40–3.80 (m, 16H), 3.30 (s, 12H). ¹³C NMR (125 MHz, CD₃CN, 298 K): δ 161.5, 160.4, 152.7, 151.6, 140.0, 128.9, 128.6, 121.4, 121.2, 120.5, 112.9,
112.1, 106.2, 100.6, 70.2, 69.8, 69.0, 68.5, 68.2, 54.3, 52.2, 49.7. MS (ESI-HRMS): m/z Calcd for \([M – 2CF_3CO_2 – H]^+\): 1309.6185; found: 1309.8259. m/z Calcd for \([M – 2CF_3CO_2]^2^+\): 655.3132; found: 655.3133.

<table>
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<th>Compound</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield</th>
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</thead>
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<tr>
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<td>1. Dean Stark / PhMe / Reflux</td>
<td>7</td>
<td>80%</td>
</tr>
<tr>
<td>7</td>
<td>2. NaBH(_4) / EtOH / RT</td>
<td>P2</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Scheme S6. Synthesis of P2**

**P2**: Compound 6 (20.0 mmol, 3 g) and 3,5-dimethoxybenzyl amine (20.0 mmol, 3.34 g) were added to a 100 mL round-bottomed flask containing C\(_6\)H\(_6\) (50 mL) and the resulting mixture was refluxed in the presence of a Dean-Stark trap for 16 h. Solvent was removed *in vacuo* and the residue was dissolved in anhydrous MeOH, NaBH\(_4\) (21 mmol, 0.72 g) was added to this solution and the reaction mixture was stirred for additional 24 h before adding H\(_2\)O (1 mL) to quench reduction. Solvent was removed *in vacuo* and the residue was taken up in H\(_2\)O (100 mL), extracted with EtOAc (3 x 100 mL), and the combined extracts were dried (Na\(_2\)SO\(_4\)), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO\(_2\), EtOAc/MeOH, 95:5) to afford 7 as a colorless viscous oil (4.8 g, 80%). \(^1\)H NMR (500 MHz, CD\(_3\)CN, 298 K): \(\delta\) 7.75 (d, \(J = 7.9\) Hz, 2H), 7.38 (d, \(J = 8.0\) Hz, 2H), 6.55 (d, \(J = 2.3\) Hz, 2H), 6.47 (t, \(J = 2.3\) Hz, 1H), 6.0 (br, s, 2H), 3.78 (m, 6H), 3.77 (s, 2H), 3.71 (s, 2H). In the next step, 7 (0.66 mmol, 0.2 g), 4-bromo-3,5-diformylpyridine (0.7 mmol, 0.15 mg), and CsF (2 mmol, 0.3 g) were added into 1,2-dimethoxyethane (100 mL) and the resulting mixture was purged with
Argon for 30 min. Pd(PPh₃)₄ (0.033 mmol, 0.038 g) was added and the mixture was heated under reflux for 1 h, cooled to room temperature, filtered over Celite and concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, CH₂Cl₂/MeOH, 97:3) to obtain P₂ as a colorless viscous oil (0.13 g, 50%). ¹H NMR (500 MHz, CD₃CN, 298 K): δ 10.2 (s, 2H), 8.45 (s, 2H), δ 7.75 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 6.55 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.3 Hz, 1H) 3.90 (s, 2H), 3.80 (br, s, 8H). ¹³C NMR (125 MHz, CDCl₃, 298 K): δ 192.7, 160.9, 153.6, 150.7, 129.3, 127.2, 127.2, 106.0, 98.9, 55.4, 53.3, 52.5. MS (ESI): m/z Calcd for [M + H]⁺: 391.43; found: 391.47.

**Scheme S7. Synthesis of DC₂·2CF₃CO₂**

DC₂·2CF₃CO₂: P₂ (0.013 mmol, 5 mg) and M (0.013 mmol, 4.8 mg) were dissolved in CD₃CN (1 mL) containing an equimolar amount of TFA and the resulting slightly yellow solution was used for characterization. ¹H NMR (500 MHz, CD₃CN, 298 K): δ 10.05 (br, s, 4H), 8.4 (s, 4H), 7.78 (s, 4H), 7.65 (d, J = 7.5 Hz, 4H), 7.38 (t, J = 7.5 Hz, 4H), 7.30 (d, J = 7.5 Hz, 4H), 7.25 (d, J = 7.5 Hz, 4H), 7.05 (d, J = 7.5 Hz, 4H), 6.92 (d, J = 7.5 Hz, 4H), 6.30 (d, J = 7.5 Hz, 4H), 6.15 (d, J = 7.5 Hz, 2H), 4.85 (m, 4H), 4.70 (m, 4H), 4.50–4.60 (m, 8H), 4.05 (br, s, 8H), 3.60–3.70 (m, 8H), 3.40–3.50 (m, 8H), 3.27 (s, 12H). ¹³C NMR (125 MHz, CD₃CN, 298 K): δ 161.7, 160.4,
152.4, 151.4, 140.4, 136.4, 131.2, 128.5, 128.1, 121.4, 120.6, 112.2, 106.2, 100.7, 71.8, 70.1, 69.8, 68.9, 68.5, 68.5, 54.2, 51.9, 51.3, 49.1. MS (ESI-HRMS): \( m/z \) Calcd for \([M-\text{CF}_3\text{CO}_2]^+\): 1575.6734; found: 1575.6778. \( m/z \) Calcd for \([M-2\text{CF}_3\text{CO}_2-\text{H}]^+\): 1461.6806; found: 1461.6880. \( m/z \) Calcd for \([M-2\text{CF}_3\text{CO}_2]^2+\): 731.3440; found: 731.3469.

3. Molecular Modeling

Figure S1: MMF94-minimized (Merck molecular force field (MMFF94) implemented in the molecular modeling software SPARTAN ‘06\(^{[33]}\)) 3D structures of DC1\(^{2+}\) showing \([\pi\cdots\pi]\) stacking interactions between dimethoxybenzyl stoppers and one of the lateral imino phenyl rings – a) top view, b) side view.
Figure S2: MMF94-minimized (Merck molecular force field (MMFF94) implemented in the molecular modeling software SPARTAN ‘06[S3]) 3D structures of DC2\textsuperscript{2+} showing [\pi\cdots\pi] stacking interactions between dimethoxybenzyl stoppers and one of the lateral imino phenyl rings – a) top view, b) side view.

4. References


5. $^1$H and $^{13}$C NMR Spectra

Figure S3: $^1$H and $^{13}$C NMR spectra of compound 3
Figure S4: $^1$H and $^{13}$C NMR spectra of compound 4
Figure S5: $^1$H and $^{13}$C NMR spectra of compound 5
Figure S6: $^1$H and $^{13}$C NMR spectra of P1
Figure S7: $^1$H and $^{13}$C NMR spectra of DC1·2CF$_3$CO$_2$
Figure S8: $^1$H NMR spectrum of compound 7
Figure S9: $^1$H and $^{13}$C NMR spectra of P2
Figure S10: $^1$H and $^{13}$C NMR spectra of DC2·2CF$_3$CO$_2$
6. Analytical High Performance Liquid Chromatography

Figure S11: Analytical RP-HPLC of a) 2, b) 4, c) 5, and d) P2; Abs @ 270 nm.